REMARKS

I. Status Summary

Claims 1-6 are pending in the present application. Election by applicants of Group I, claims 1-6 has been acknowledged by the U.S. Patent and Trademark Office (hereinafter "the Patent Office") and claims 1-6 are presently examined. Claims 8-27 have been withdrawn from prosecution at this time. Claims 1, 2, 3 and 5 have been amended and new claims 29-30 have been added. Claims 7 and 28 have been canceled. No new matter has been added.

The specification has been objected to for the presence of an embedded hyperlink and for the use of trademarks without capitalization.

Claims 1-5 presently stand rejected under 35 USC § 102(e) as allegedly being anticipated by U.S. Patent No. 6,551,784 to Fodor et al. (hereinafter "Fodor et al."). Claims 1-6 presently stand rejected under 35 USC § 102(a) as allegedly being anticipated by the journal article of Tseng et al. (*Nucleic Acids Research*, Vol. 29, No. 12, pp. 2249-57, 2001; hereinafter "Tseng et al").

II. Response to Objection to Specification

The specification has been amended as indicated by the amendment above to delete the embedded hyperlink and to provide trademarked names in capital letters. No new matter has been added. In view of the above amendments, applicants respectfully request withdrawal of the objections to the specification.

III. Response to the Rejections Under 35 U.S.C. § 102

Claims 1-5 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Fodor et al. and claims 1-6 have been rejected under U.S.C. § 102(a) as allegedly being anticipated by Tseng et al.

IIIA. § 102(e) rejection of claims 1-5.

The Patent Office contends Fodor et al. teach a method of assessing the variability of observed signals from probes on a microarray by determining the

average signal intensity from control probes on an array obtained from intrinsically multiple hybridizations and using the average to calculate a correction coefficient equal to a constant. The Patent Office further contends Fodor et al. teach the determination of the coefficient of variation known in the art to be the ratio of the standard deviation divided by the average and the use of the statistical measure to regulate the removal of data which do not fit a determined value. The Patent Office therefore contends Fodor et al. teach every step of each of rejected claims 1-5.

The position of the Patent Office as summarized above with respect to claims 1-5 is respectfully traversed as described below.

"A claim is anticipated only if each and every element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Independent claim 1 presently recites a method for correcting oligo probe hybridization signals, comprising measuring signals from each oligo probe during multiple hybridizations within a linear range; calculating a correction coefficient for each oligo probe by requiring its signal average to be equal to a constant; and correcting the signal for each oligo probe using the calculated correction coefficient. Applicants respectfully disagree with the Patent Office's interpretation that the teachings of Fodor et al. anticipate every element of present claim 1.

Claim 1 has been amended at the preamble to more particularly recite that oligo probe hybridization signals are being corrected. The phrase "determining an uncertainty coefficient for each oligo probe" has been deleted from Claim 1. In addition, claim 1 is amended to more particularly recite in part that the signal for each oligo probe is corrected using the calculated correction coefficient. Support for the amendments can be found throughout the drawings and specification, including, for example, at the Abstract and at Figures 1, 2 and 4 as filed. As such, no new matter has been added by the amendment.

Dependent claim 3 presently recites a method for correcting oligo probe hybridization signals, comprising determining an uncertainty coefficient for each oligo probe. Applicants respectfully disagree with the Patent Office's interpretation that the teachings of Fodor et al. anticipate every element of present claim 3.

Claim 3 has been amended in part by deleting the phrase "wherein the correction coefficients are calculated based on requiring its signal average to be equal to a constant", as this language is present in original and currently amended claim 1. Claim 3 is amended by insertion of the phrase "comprising determining an uncertainty coefficient for each oligo probe". Support for the amendment can be found throughout the drawings and specification including, for example, at claim 1 as originally filed. As such, no new matter has been added by the amendment.

New dependent claim 29 recites a method for correcting oligo probe hybridization signals, wherein the multiple hybridizations are with genomic DNA. Support for new claim 29 can be found throughout the drawings and specification as originally filed including, for example, at the Abstract; at original claims 8 and 14; at page 2, lines 3-5, and at page 4, lines 4-9, of the specification; and at Figure 1. As such, no new matter has been added by the amendment.

New dependent claim 30 recites a method for using the corrected oligo probe hybridization signals to calculate an expression level for a gene, comprising calculating a weighting factor and using the weighting factor to determine the expression value for the gene. Support for new claim 29 can be found throughout the drawings and specification as originally filed including, for example, at Figure 2. As such, no new matter has been added by the amendment.

Applicants respectfully assert that Fodor et al. fail to teach the measurement of signals from *each* oligo probe during multiple hybridizations and requiring the signal average to be equal to a constant, as recited in amended independent claim 1. The section of Fodor et al. (col. 36, l. 15-20) referred to at page 4 of the Official Action describes the use of normalization probes to control for variations in hybridization conditions. In Fodor et al., to obtain normalization, control probes that are

complementary to control sequences are added in a known concentration to the array. Hybridization signals are then measured for both the control probes and other probes in the array (non-control probes). Normalization is obtained by dividing the measured signal from the non-control probes by the average signal produced by the normalization controls. This is in contrast to the recitation in claim 1 of measuring signals from *each* oligo probe during multiple hybridizations within a linear range, and calculating a correction coefficient for *each* oligo probe by requiring its signal average to be equal to a constant. Unlike in Fodor et al., the signal average recited in claim 1 is referring to an average signal for *each individual* oligo probe, and not a relative measurement of the signals of non-control probes to the average signal of a number of control probes. Accordingly, Fodor et al. do not teach a method for calculating a correction coefficient for each oligo probe. As such, Fodor et al. fail to teach each and every element of independent claim 1.

It is further contended at page 4 of the Official Action that determining the coefficient of variation is taught at column 4, lines 13-21, of Fodor et al. While the use of the measurement of a coefficient of variation (the standard deviation divided by the average) appears to be described at column 4, lines 13-21, of Fodor et al., this coefficient of variation is measured for the hybridization intensity averaged over *at least 5* oligonucleotide probes for each gene on the array for which expression is to be detected. This is in marked contrast to dependent claims 2, 3 and 4, where an uncertainty coefficient, which is the ratio of the average to the standard deviation, is determined for *each* oligo probe. Unlike in Fodor et al. the uncertainty coefficient recited in dependent claims 2, 3 and 4 is for *each individual* oligo probe, and not for *at least 5* different oligonucleotide probes for each gene. Accordingly, Fodor et al. do not teach a method for calculating an uncertainty coefficient for each oligo probe. As such, Fodor et al. fail to teach each and every element of dependent claims 2, 3 and 4.

It is further asserted at page 4 of the Official Action that Fodor et al. at column 49, lines 63-69, describe the use of a coefficient of variation statistical measure for

regulating the removal of data. In fact, lines 63-69 of column 49 are actually directed to the analysis of polymers synthesized in squares on the substrate and, thus, Applicants believe that this may be a typographical error. Instead, columns 38-43 of Fodor et al. describe the use of P values to determine gene expression. In particular, column 39, lines 63-67, through column 40, lines 1-4, describe the use of P values to determine whether gene expression is present (expressed), marginal, or absent (not expressed). The P values in Fodor et al. are based on a comparison of hybridization signals obtained for a perfect match probe ('PM') and a mismatch probe ('MM') for the same target oligonucleotide probe on the array. Column 38, lines 61-67, of Fodor et al. describe the use of threshold values by determining whether the difference between the hybridization intensities of a pair (I_{pm} - I_{mm}) is greater than or equal to the difference threshold, and whether the quotient of the hybridization intensities of the pair (I_{pm}/I_{mm}) is greater than or equal to the ratio threshold. The use of threshold values in Fodor et al. to inform the decision of whether to remove data at best involves using a comparison of a perfect match to a mismatch probe. This is in marked contrast to dependent claim 5, where the decision of whether to redesign or disregard a probe is based on whether the individual probe's signal has an uncertainty coefficient greater than a predetermined value. As such, Fodor et al. do not teach the same use of coefficient of variation as recited in claim 5.

The dependence of Fodor et al. on the use of comparative hybridization signal intensities between perfect match and mismatch probes to measure gene expression is further illustrated in the Example beginning at column 99. In this Example, methods are described for quantitative analysis of hybridization patterns and intensities (col. 102), optimization of probe selection (col. 102), specificity of hybridization (col. 103), detection of gene expression levels in a complex target sample (col. 103), and relationship between target concentration and hybridization signal (col. 104). Each of these technologies is based on the comparison of hybridization signal intensities between perfect match and mismatch probes. For example, column 102, lines 36-39, describe selection of probes using the *difference*

in intensity between a probe and its corresponding mismatch probe which exceeds a threshold limit. Column 102, lines 53-54, describe how the signal for a particular gene was counted as the average difference (PM - MM control) *for the selected probes* for each gene. In marked contrast, dependent claim 5 is recites use of an uncertainty coefficient for *individual* probes. Fodor et al. further describe at column 103, lines 15-19, how the mismatch probe of each pair served as an internal control for hybridization specificity. Here, the analysis of PM/MM pairs at best allowed low intensity hybridization patterns from rare RNAs to be recognized in the presence of cross-hybridization signals. As illustrated by the foregoing examples, Fodor et al. do not teach the method recited in claim 5 for deciding whether to redesign or disregard a probe having an uncertainty coefficient greater than a predetermined value, where the uncertainty coefficient is that of the *individual* probe. As such, Fodor et al. do not teach each and every element of claim 5.

Since Fodor et al. do not teach each and every element of claims 1-5, applicants respectfully request withdrawal of the rejection of claims 1-5 under 35 U.S.C. § 102(e) as being anticipated by Fodor et al. Allowance of claims 1-5 is also respectfully requested.

IIIB. § 102(a) rejection of claims 1-6.

Applicants respectfully traverse this rejection. In response to the 35 U.S.C. §102(a) rejection, applicants respectfully submit the attached Declaration under 37 CFR §1.131 regarding Tseng et al. Summarily, the attached Declaration establishes that the inventive subject matter of claims 1-6 was invented prior to the publication date of Tseng et al., which is necessarily no earlier than the April 11, 2001, acceptance date of the journal article. Consequently, it is respectfully submitted that the rejection of claims 1-6 under 35 U.S.C. §102(a) as being anticipated by Tseng et al. has now been rendered moot. It is therefore respectfully requested that Tseng et al. as a reference be withdrawn, and hence, that the rejection be withdrawn.

Accordingly, applicants respectfully request withdrawal of the rejection of claims 1-6 on the basis of the attached Declaration. Allowance of claims 1-6 is also respectfully requested.

CONCLUSION

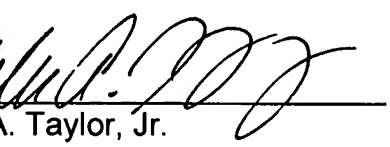
In light of the above remarks and the enclosed 131 affidavit, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any additional fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: June 7, 2007 By: 

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